REMARKS

The expression "ED-B" is a well recognized one and is the proper name for the domain of fibronectin which is involved. See the cited Neri et al. PCT publication, for example, as well as the rest of the prior art of record. Where a term requires no definition, it is not indefinite.

In view of the foregoing clarification of the claims by which the affinity of the antibodies is now more clearly recited as less than about 54pM, the prior art rejection should be withdrawn. Note that 54pM is the affinity of the antibody L19. See Table 2 of the application, for instance. This is not to imply that any of the scope of the subject matter of this application is not patentable. It is indeed presently intended to seek a broader literal scope in continuing applications.

Old mis-formatted page 27 has been replaced with new page 27, which is properly formatted. As for the sequence objections, these are the result of an apparent overlooking of the sequence disclosure-related amendments submitted on September 1, 2000. If these overlooked amendments are made with respect to the new page 27 (and page 14), all objections will be overcome.

The new recitations regarding mutations are clearly supported in the paragraph of the specification bridging pages 7 and 8, for example, as well as the examples. Note, for instance, example 2, pages 16 and 17 describing the mutations in the H10 antibody which led to the L19 antibody (a random mutation at position 32 in CDR1 of the VL and a random mutation at position 50 in CDR2 of the VL). Previously (pages 22-23), mutations in positions 50, 52 and 54 in CDR2 of the VH's of prior clones were used to generate improved affinity antibodies, e.g., leading to H10 (page 23, lines 8-9.) Other mutations earlier in the process are described on page 22. These descriptions clearly support the newly added claims drawn to mutations.

DETAILED ACTION

Claims 14-17, 19-27, 28-39 are pending.

Claims 20-24 and 28-39 are under consideration.

Claims 14-17, 19 and 25-27 stand withdrawn from consideration.

The text of applied statutes has been made of record in a prior Office Action.

Request for Continued Examination

1. The request filed on December 12, 2003 is acceptable and an RCE has been established. An action follows.

Allowable Subject Matter

2. Claim 38 is objected to as being dependent upon a rejected base claim, but would be allowable if rewritten in independent form including all of the limitations of the base claim and any intervening claims.

Rejections Maintained

3. Claims 20-24 rejected under 35 U.S.C. 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention because claim 20 still recites the an abbreviation "ED-B" for reasons of record in paper number 15, paragraph 15, subparagraph c.

4. Claims 20-23, new claims 33, 34 and 35((see Neri et al, page 23, line 35, figure 1b, alignment, aa 94-96) are rejected under 35 U.S.C. 102(b) as being anticipated by **Neri et al** (WO97/45544, reference provided in Applicant's 1449) for reasons of record in paper number 15, paragraph 12.

5. Claims 20-24, and new claims 28-37 and 39 are rejected under 35 U.S.C. 103(a) as being unpatentable over Neri et al (WO97/45544, reference provided in Applicant's 1449) in view of Theodore et al (US Pat. 6,015,897)for reasons of record in paper number 15, paragraph 16.

Specification

6. The title of the invention is still not descriptive. A new title is required that is clearly indicative of the invention to which the claims are directed. Reference to Fibronectin extra domain B would describe the invention more clearly.

7. The Brief Description of the Drawings and the figures shown do not evidence clear labels and description of the contents of the figures see 37 CFR 1.74, 37 CFR 1.81, 1.83-1.85, and MPEP § 608.02.

1. Figure 1A & 1B should be recited and briefly described.

2. Figure 2A & 2B should be recited and briefly described.

3. Figure 3 A,B &C should be recited and briefly described.

4. Figure 4 A,B &C should be recited and briefly described

5. Figure 7, each frame (A-H) should be labeled and briefly described. Figure 7 shows several abbreviations. These abbreviations should be defined in the Brief Description of the Drawings. Clarification of the abbreviations is requested.

6. Figure 9 A,B &C should be recited and briefly described.

7. Figure 10 A,B, C & D should be recited and briefly described.

8. Figure 11 A, B,C,D,E,F,G,H,I,J,K & L should be recited and briefly described.

9. Figure 12 A, B,C,D,E,F,G,H,I,J,K & L should be recited and briefly described.

Response to Arguments

8. Applicant's arguments filed March 28, 2001 have been fully considered but they are not persuasive.

9. The rejection of claims 20-23 and new claims 33-35 rejected under 35 U.S.C. 102(b) as being anticipated by Neri et al, is argued by asserting the antibodies do not exhibit high affinity for the ED-B domain, that a dissociation constant of $6X\ 10^{-8}$ is not high affinity and is not in the subnanomolar range as recited in claims 28-32.

10. It is the position of the examiner that Neri et al claims antibodies of 6X 10^{-8} or **LESS** (see claim 14, page 44). The antibody binding specificities are claimed with an upper limit and no lower limit, thus clearly defining antibodies with high affinity for ED-B. The smaller the dissociation constant, the higher the binding. With respect to newly submitted claims 33-35, Neri disclosed scFv antibodies, recombinantly produced with a limited number of mutations shown in figure 1B. The rejection is maintained for reasons of record in paper number 15, paragraph 12.

11. The rejection of claims 20-24, and new claims 28-37 and 39 under 35 U.S.C. 103(a) as being unpatentable over Neri et al (WO97/45544) in view of Theodore et al (US Pat. 6,015,897) is asserted as not obviating the claimed invention based upon the recitation of the phrase "high affinity for ED-B domain"in all of the claims. Applicant provided a reference to Viti et al (1999) to show "the desirability of high affinity for the angiogenic properties of the antibody."

12. It is the position of the examiner that Neri et al does disclose antibodies with high binding affinity for ED-B. Neri et al recites a range of binding specificities of 6X 10^{-8} or **LESS** (see claim 14, page 44). The Neri reference clearly discloses antibodies with high binding specificity and suggests the selection of antibodies with subnanomolar binding specificities through the recitation of the phrase 6X 10^{-8} or **LESS** in claim 14. The person of ordinary skill in the art would have been motivated to select antibodies with binding specificities in the subnanomolar range because Neri et al teaches that antibodies with high binding specificities to the ED-B domain provide the medical professional with a reagent that will identify cancerous tissue and can be used as a antibody conjugate in method of delivering cytotoxic agents.

With respect Viti et al, reference provided by Applicant attached to the Amendment submitted March 28, 2001, the antibody, designated "L19" of the reference, it is the position of the examiner that this antibody is not claimed, except in claim 38. Claim 38 has been designated as containing allowable subject matter. Claims 20-24, 28-37 and 39 do not recite the novel and unobvious amino acid sequence, nor the specific binding affinity for the ED-B domain of fibronectin of antibody L19. Neri in view of Theodore is maintained for reasons of record in paper number 15, paragraph 16.

New Claims/New Claim Limitations/New Grounds of Rejection

Specification

13. The disclosure is objected to because of the following informalities: At page 14, lines 13-20, the nucleic acid sequence and amino acid sequence recited at this location are confusing due to the sequences appearing to be 4 sequences and only two Seq ID Nos shown. Clarification of the sequences is requested.

Table 1, page 27, recites amino acid sequence which should be designated with SEQ ID Nos. to place the application in sequence compliance. Any amino acid sequence of four amino acids or more must be given a SEQ ID NO or reference a larger sequence. Appropriate correction is required.

Claim Rejections - 35 U.S.C. § 112

14. The following is a quotation of the second paragraph of 35 U.S.C. 112:

> The specification shall conclude with one or more claims particularly pointing out and distinctly claiming the subject matter which the applicant regards as his invention.

15. Claims 20, 35-36 are rejected under 35 U..S.C. 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention.

16. The term "high affinity for the ED-B domain" in claim 20 is a relative term which renders the claim indefinite. The term ""high affinity for the ED-B domain" is not defined by the claim, the specification does not provide a standard for ascertaining the requisite degree, and one of ordinary skill in the art would not be reasonably apprised of the scope of the invention.

Claim 35 recites the phrase "limited number of mutations". As no upper limit is recited, what is intended is not distinctly claimed. What type of mutations have been introduced? Claim 35 also recites the phrase "mutations in its CDR residues". As these letters are representative of amino acids, clarification of this phrase is requested.

Claim 36 recites specific residues in two domains of the antibodies that have been mutated, but the number of amino acids contained in the antibodies of claim 35 has not been defined. The number of amino acids in the recombinant antibodies can differ, and therefore would evidence different numbering schemes. If all of the antibodies comprise the same number of amino acids, amendment of the claim with the SEQ ID NO for the amino acid sequence for the antibody or to define the specific number of amino acids in the antibody would clarify the reference points recited in claim 36, a parent reference sequence has not been defined in the claims.

Claim 36 recites "VH" and "VL", as these letters are designators for amino acids. Clarification of the meaning of these abbreviations is requested.

Conclusion

17. This is a non-final action.

18.

Any inquiry concerning this communication or earlier communications from the examiner should be directed to Ginny Portner whose telephone number is (571)272-0862. The examiner can normally be reached on Monday through Friday from 7:30 AM to 5:00 PM except for the first Friday of each two week period.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Lynette Smith, can be reached on (571) 272-0864. The Group and/or Art Unit location of your application in the PTO will be Group Art Unit 1645. To aid in correlating any papers for this application, all further correspondence regarding this application should be directed to this Art Unit.

Vgp

May 13, 2004

L. F. Smith

LYNETTE R. F. SMITH
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ART UNIT	**PAPER NUMBER**
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DATE MAILED: 05/17/2004

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Please find below and/or attached an Office communication concerning this application or proceeding.

Office Action Summary	Application No.	Applicant(s)	
	09/300,425	NERI ET AL.	
	Examiner	Art Unit	
	Ginny Portner	1645	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If the period for reply specified above is less than thirty (30) days, a reply within the statutory minimum of thirty (30) days will be considered timely.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☐ Responsive to communication(s) filed on *12 December 2003*.

2a)☐ This action is **FINAL**. 2b)☒ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☐ Claim(s) *14-17 and 19-39* is/are pending in the application.

4a) Of the above claim(s) *14-17,19 and 25-27* is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☐ Claim(s) *20-24, 28-39* is/are rejected.

7)☐ Claim(s) *38* is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

12)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

1) ☐ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☒ Information Disclosure Statement(s) (PTO-1449 or PTO/SB/08) Paper No(s)/Mail Date _____.
4) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____.
5) ☐ Notice of Informal Patent Application (PTO-152)
6) ☐ Other: _____.